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Evaluation of worldwide clinical trials by gender: An FDA perspective

Emily Ayuso[a], Ruth J. Geller[a], Junyang Wang[b], John Whyte[b], Marjorie Jenkins[a,*]

[a] Office of Women's Health, OC, FDA (Address: 10903 New Hampshire Avenue, WO32-2333, Silver Spring, MD 20993, USA
[b] Professional Affairs and Stakeholder Engagement, CDER, FDA (Address: 10903 New Hampshire Avenue, Bldg. 51, Rm 2341, Silver Spring, MD 20993-0002, USA

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ABSTRACT

Introduction: The US Food and Drug Administration (FDA) has undertaken efforts to promote representation of women in clinical trials. The objectives of this research are to assess women's participation in clinical trials from a global perspective and to analyze the demographic characteristics of clinical trial participants.

Methods: FDA's Center for Drug Evaluation and Research-Professional Affairs and Stakeholder Engagement (CDER/PASE) and Office of Women's Health (OWH) collaborated to evaluate demographic data (race, ethnicity, gender, and age) of pivotal trials of New Molecular Entities (NMEs) approved in 2015–2016 by geographic location. One hundred fifty-four pivotal clinical trials supporting 66 NMEs were identified, and the research team analyzed demographic characteristics of 131,749 participants from 70 countries.

Results: U.S. sites contributed 31% of the 131,749 study participants. On the country level, the United States contributed the largest number of participants and other individual countries contributed 5% or less of the total trial population. Overall, 43% (n = 56,272) of the 131,747 clinical trial participants were women. Of the 40,833 U.S. participants, 49% were women as compared to 40% of the 90,914 non-U.S. participants. Similar levels of participation were seen after the exclusion of sex-specific drug indications, and by therapeutic area for U.S. and non-U.S. sites.

Conclusions: Clinical trials are becoming increasingly multi-national, and the increasing representation of women across countries is promising. FDA approval processes ensure that global data used in the drug approval process meets regulatory standards and that data can be generalized to the U.S. population.

1. Introduction

Established in 1906, the U.S. Food and Drug Administration (FDA) is the oldest consumer protection agency in the country. As a regulatory agency, its mission is to protect the public's health by ensuring the efficacy and safety of human and veterinary drugs, biological products and medical devices; ensuring the safety of the nation's food supply, cosmetics, and products that emit radiation; and regulating manufacturing, marketing and distribution of tobacco and tobacco-products. Inclusion of women in clinical trials is a key focus of FDA as part of its scientific and public health mission. The agency has undertaken a multitude of efforts to promote representation of women in clinical trials including guidance and regulation.

FDA guidance documents provide policy recommendations about the collection and analysis of subgroup data in clinical trials. In 1977, FDA issued guidance recommending excluding women of childbearing potential from early clinical trials. However, in 1993 FDA overturned this policy by issuing the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs [1]. Here the FDA encouraged participation of women in Phase I and II trials for drugs used by both men and women and required the inclusion of women in efficacy studies and analysis of data on sex differences. The guidance recommended that effects of menstrual status, concomitant estrogen treatment, and hormonal contraceptives on drug pharmacokinetics be recorded. This was followed by a key FDA regulation, the 1998 “Demographic Rule”, which required sponsors to tabulate trial population by age, gender and race on Investigational New Drug (IND) applications, and to analyze safety and efficacy by age, race, gender,

Abbreviations: FDA, Food and Drug Administration; OWH, Office of Women's Health; CDER, Center for Drug Evaluation and Research; PASE, Professional Affairs and Stakeholder Engagement; NDA, New Drug Application; ICH, International Council for Harmonization; IND, Investigational New Drug; GAO, Government Accountability Office; FDASIA, Food and Drug Administration Safety and Innovation Act; CVD, Cardiovascular Disease; NME, New Molecular Entity; ICH, International Conference on Harmonization; NIH, National Institutes of Health; ORWH, Office of Research on Women's Health

* Corresponding author at: 240-402-3930, 10903 New Hampshire Avenue, Building 32 Room 2333, Silver Spring, MD 20993, USA.
E-mail addresses: Emily.ayuso@fda.hhs.gov (E. Ayuso), ruthjgeller@gmail.com (R.J. Geller), Junyang.Wang@fda.hhs.gov (J. Wang), Jwhyte@webmd.net (J. Whyte), Marjorie.jenkins@fda.hhs.gov (M. Jenkins).

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and other variables as deemed appropriate on New Drug Application (NDAs).

Overall, participation of women in clinical trials has increased over time. The 1992 Governmental Accountability Office (GAO) Report noted for late phase drug and biologic clinical trials for non-sex specific products, women's participation was 44%. [2] [3]. Following this, a 2001 GAO report stated that women were included in pivotal clinical trials at sufficient levels to determine effectiveness of every NDA in women and that women comprised the majority of clinical drug trial participants for over half of the NDAs reviewed [4]. In late phase drug and biologic clinical trials for non-sex specific products approved 2007–2009, women's participation was nearly 50%. The Food and Drug Administration Safety and Innovation Act (FDASIA)[1] Section 907 report stated that sex analysis and reporting was most consistently reported in medical product applications, compared to race, ethnicity and age reporting [5]. The FDASIA Sec. 907 report further affirmed that for approved drugs, representation of patients in clinical trials by age and sex reflected the disease indication studied [5]. In phase 1, 2, and 3 trials for NDA and BLAs approved 2013–2015, race reporting was consistently high (97.5%); however, ethnicity reporting was limited and inconsistent (64.7%) [6]. In particular, “Hispanic/Latino” was reported as a race designation in some and an ethnicity designation in others [6]. Overall, some racial minorities including Black/African American patients are still not well represented in drug development programs [6]. Continued efforts are needed to ensure that clinical trial participants are demographically representative of disease populations. This objective of this evaluation is to assess women's participation in clinical trials from a global perspective and provide an analysis of the demographic characteristics of participants in pivotal trials of recently approved New Molecular Entities (NMEs).

2. Methods

FDA's Center for Drug Evaluation and Research-Professional Affairs and Stakeholder Engagement (CDER/PASE) and the Office of Women's Health (OWH) collaborated to evaluate the demographic data (race, ethnicity, gender, and age) of pivotal trials for NMEs approved in 2015–2016 by geographic location. One hundred and fifty-four pivotal clinical trials supporting 66 NMEs were identified, and the research team analyzed the demographic characteristics of 131,749 participants from 70 countries using JMP software (SAS Institute Inc., Cary, NC). The research team used patient-level data from the FDA Document Archiving, Reporting, and Regulating Tracking System (DARRTS) and trial-level data from Data Analysis and Search Host (DASH) and Data Analysis and Search Host-Demographics (D-DASH). This paper focused on analyzing the global gender data. As clinical trials report the self-identified gender, not biological sex, of participants, we refer to participants as men or women (gender) rather than male or female (sex).

3. Results

Of 131,749 study participants, 31% participated at U.S. clinical trial sites. On the country level, the U.S. contributed the largest number of participants and other individual countries contributed 5% or less of the total trial population. Globally, 43% (n = 56,272) of the 131,747 clinical trial participants were women (gender was not reported for 2 participants). Of the 56,272 women, 20,053 (36%) were from the U.S. The participation of women differed between the U.S. and non-U.S. sites (Fig. 1), with higher participation of women observed in the U.S. Forty-nine percent of the 40,835 U.S. participants were women, compared to 40% of the 90,914 non-U.S. participants. Similar levels of participation were seen across therapeutic areas for the U.S. and non-U.S. sites.

To remove the influence of drugs indicated for sex-specific disease areas (e.g. ovarian cancer), we excluded approvals for sex-specific indications. There were 7 trials for sex-specific indications: [obstetrics and gynecology] (N = 3), [medical imaging and diagnostics] (N = 1), [oncology] (N = 3), where N = number of trials. Similar levels of participation by gender were observed after the exclusion of sex-specific drug indications. Globally, women represented 41% (n = 52,082) of the 127,458 participants in clinical trials for non-sex specific indications. Of the 52,082 women in clinical trials for non- sex-specific indications, 16,715 (32%) were from the U.S. Within the U.S., 45% (n = 16,715) of the 37,396 participants in clinical trials for non-sex specific indications were women compared to 39% (n = 35,367) of the 90,062 participants outside the U.S. With the exclusion of sex-specific indications, global participation of women varied by therapeutic area ranging from 0% (diagnostic medical imaging therapeutic area; n = 0 of the 99 clinical trial participants) to 76% (ophthalmology; n = 1713 of the 2249 clinical trial participants) with a median of 44% (Fig. 2).

Although progress has been made in the inclusion of women in trials, further progress is needed in racial and ethnic diversity. For example, the majority (79%) of 18,960 women who participated in CVD trials were white (Fig. 3).

The representation of Hispanic women and Black women ranged from 8% and 2–5% of women participants, respectively, across indications for cardiovascular disease (CVD) trials. Participation of Asian women ranged from 1 to 22% across indications and varied by trial site location; overall, 6.5% of women participants in CVD clinical trials were located in Asia. Most CVD trials were conducted mainly in European countries and 84% of CVD trial participants were at sites outside the U.S. CVD trials were also conducted in South Africa and in Latin American countries including Venezuela, Peru, Panama, Mexico, Guatemala, Chile, Ecuador, Brazil, and Argentina.

The U.S. contributed the most women (20,053) from a single country; countries that contributed the most women following the U.S. were Russia, Germany and Poland with similar numbers of enrolled women (ranging from 2894 to 2152) (Table 1).

On the country level, representation of women in clinical trials ranged from 34% to 49%, with the highest participation of women observed in the U.S. (49.1%) followed by France (46.1%), South Korea (45.8%), and Canada (45.2%).

4. Discussion and conclusion

We found that women comprised 43% of all clinical trial participants for NMEs approved from 2015 to 2016 with similar levels after the exclusion of sex-specific indications (41%). It is important not only to assess the level of participation of women but also the geographical location and generalizability of data. The large numbers of clinical trial participants in Russia, Germany, and Poland likely reflect recent investment in the clinical trial infrastructure [7] [8,9]. As clinical trials are becoming increasingly multi-national, the representation of women across countries is promising. However, additional progress is needed to ensure increasing diversity within race and ethnicity as well as gender. From the data gathered, it is important to acknowledge that women were included in clinical trials at varying levels across geographic sites. From a global health perspective, it is important to ensure women's participation is wide, and representative of disease populations.

FDA's efforts to address concerns and support for the inclusion of women and minority groups in clinical trials are ongoing. In 2015, an FDA initiative, Drug Trials Snapshots was launched to provide consumers with information pertaining to differences in benefits and side effects of new FDA approved drugs between sex, race and age groups.

[1] FDASIA Section 907 directed FDA to investigate the inclusion of demographic subgroups (defined by sex, race, age, and ethnicity) in clinical trials in applications for medical products (drugs, biologics, and devices) submitted to the FDA for approval and the availability of subgroup-specific safety and effectiveness data. FDA examined 72 medical products submitted for marketing approval in 2011. [5]

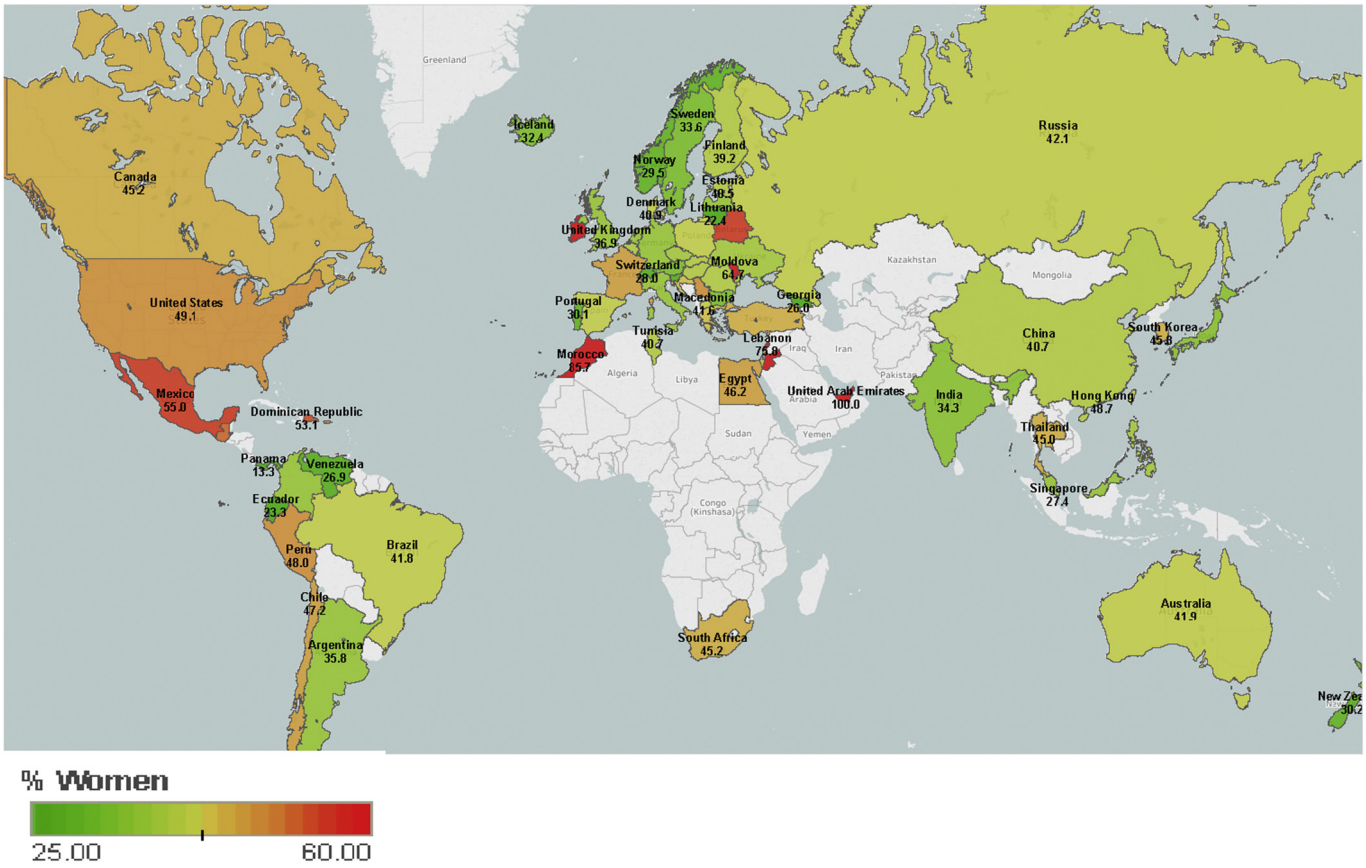

Fig. 1. Percent women among trial participants by country. Map based on Longitude and Latitude. Color shows % women among total clinical trial participants within a country.

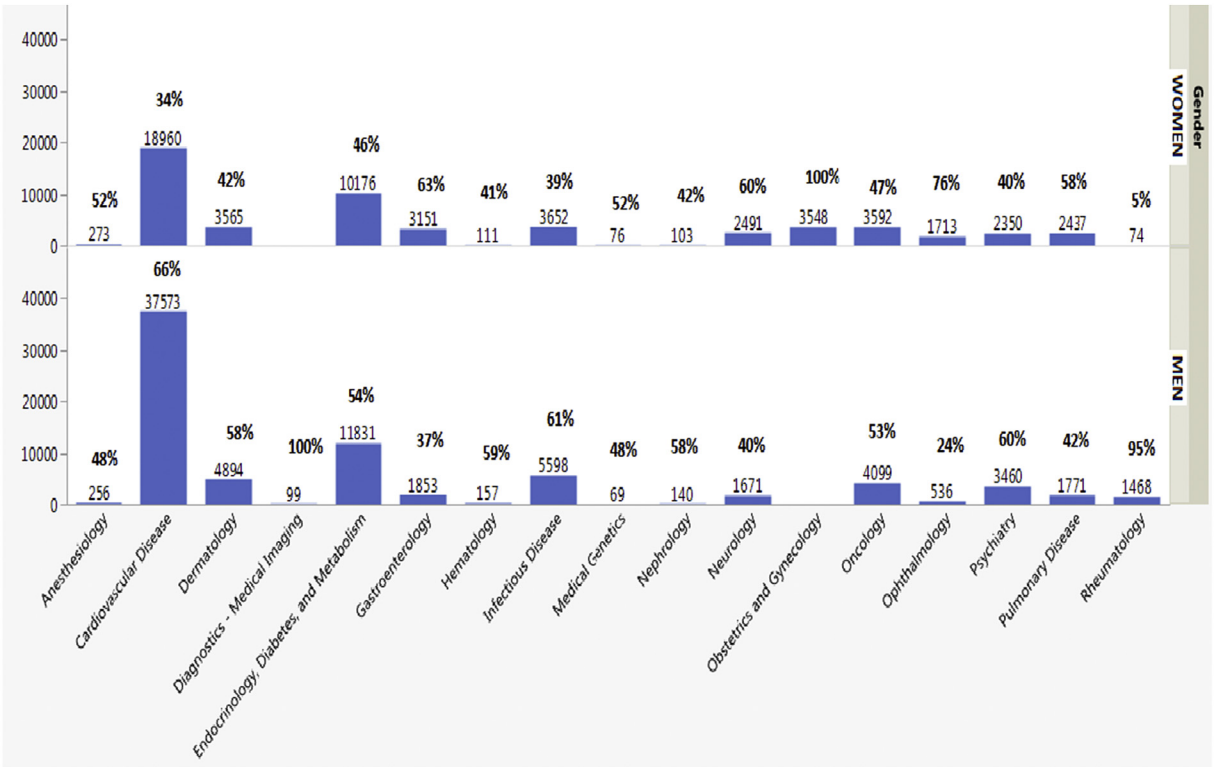

Fig. 2. Number of women and men within therapeutic area. Percent participation by gender is listed for each therapeutic area.

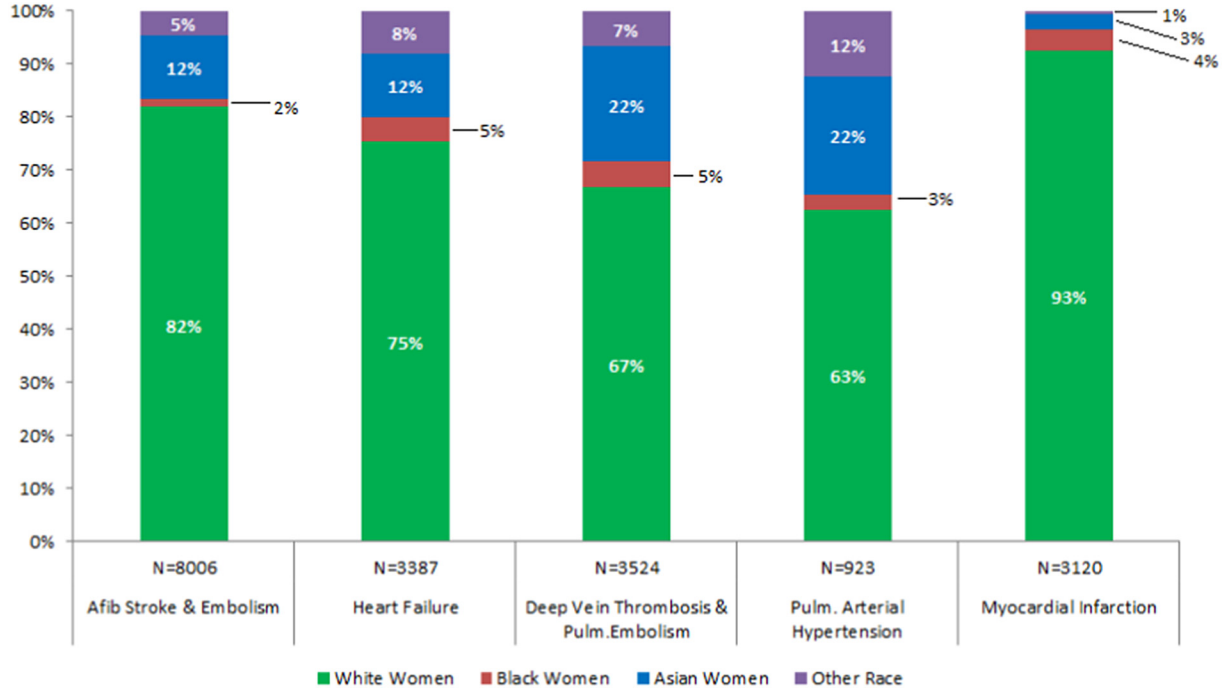

Fig. 3. Women in CVD Trials across Indications. N = 18,960 women in CVD trials.

Table 1
Representation of women in trials, in the 20 countries with highest overall enrollment. Countries are listed in descending order of total enrollment.

Country	Total Women	Total Enrolled	% Women per country
United States	20,053	40,835	49.1%
Russia	2894	6875	42.1%
Germany	2150	5802	37.1%
Poland	2152	5170	41.6%
Czechia	1884	4858	38.8%
Canada	2147	4748	45.2%
India	1318	3841	34.3%
Ukraine	1343	3551	37.8%
France	1402	3040	46.1%
Hungary	1140	2887	39.5%
Japan	993	2878	34.5%
United Kingdom	1061	2872	36.9%
Italy	996	2703	36.8%
Romania	929	2375	39.1%
Bulgaria	789	2364	33.4%
Spain	952	2316	41.1%
Argentina	808	2255	35.8%
China	918	2254	40.7%
Brazil	865	2070	41.8%
South Korea	930	2030	45.8%

The Women's Health Research Roadmap, launched in 2016, provides a plan with seven priority areas emphasizing the importance of new and enhanced research to FDA regulatory decision making on products that impact women's health. The Diverse Women in Clinical Trials Initiative, launched in 2016, is a collaborative effort between OWH and the NIH Office of Research on Women's Health (ORWH) to raise awareness about the importance of participation of diverse women in research and provides best practices on recruitment, study design, and subpopulation analysis. FDA's OWH also funds research, trainings, and workshops to further the development of policy and regulation that impact women's health.

Clinical trials are becoming increasingly multinational [10]. Accordingly, in this study of participation in pivotal trials of recently approved NMEs, the majority of clinical trial participants were from trial sites outside the U.S. Published literature suggests that the growth of global clinical trials could be due to multiple factors such as accessibility, feasibility, and industry activities [11–13]. FDA approval processes ensure that global data used in the drug approval process meet regulatory standards and that the data can be generalized to the U.S. population [14]. As FDA is a founding regulatory member of the global harmonization process via the International Council for Harmonization (ICH), FDA is committed, with the combined efforts of regulatory and industry agencies worldwide, to ensuring the harmonization and rationalization of regulation for public health through the implementation of ICH guidance documents [15]. This global initiative is committed to achieving greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner [15].

Limitations to the collection of demographic data in global clinical trials exist. Sex, as defined by the National Institutes of Health and the Canadian Institutes of Health, is a biological variable defined by chromosomes and is determined by genetic evaluation [16]. A person's self-identity, based on social, environmental, cultural, and behavioral factors defines gender [16]. As clinical trial demographics reflect self-reported gender, not sex, of study participants, we can only evaluate representation by gender. Ethnicity data is frequently missing from non-U.S. sites, making it difficult to draw conclusions from data percentages. Race and ethnicity categories are also defined differently across countries, impeding global comparison of racial and ethnic participation data. Demographic categories based on the U.S. population may have limited applicability to other geographic regions. Additionally, there is significant heterogeneity within racial and ethnic categories. Improved standards for demographic data collection and more specific demographic terminology could aid in better understanding clinical trial demographics and generalizability. Finally, our analysis was limited to pivotal trials for NMEs approved by FDA in 2015–2016; this is only a subset of all drug trials conducted globally.

Conflict of interest

The authors declare no conflict of interest

Appendix A. List of Therapeutic Area with number (N) of total clinical trial participants in sex-specific trial. Shown also as percent of total clinical trial enrollment

Therapeutic area	Non sex-specific		Sex-specific	
	N	% of Total	N	% of Total
Anesthesiology	529	0.40%	0	0.00%
Cardiovascular Disease	56,533	42.9%	0	0.00%
Dermatology	8459	6.42%	0	0.00%
Diagnostics- Medical Imaging	0	0.00%	99	0.08%
Endocrinology, Diabetes, and Metabolism	22,007	16.7%	0	0.00%
Gastroenterology	5006	3.80%	0	0.00%
Hematology	268	0.20%	0	0.00%
Infectious Disease	9250	7.02%	0	0.00%
Medical Genetics	145	0.11%	0	0.00%
Nephrology	243	0.18%	0	0.00%
Neurology	4162	3.16%	0	0.00%
Obstetrics and Gynecology	0	0.00%	3548	2.69%
Oncology	7049	5.35%	642	0.49%
Ophthalmology	2249	1.71%	0	0.00%
Psychiatry	5810	4.41%	0	0.00%
Pulmonary Disease	4208	3.19%	0	0.00%
Rheumatology	1542	1.17%	0	0.00%

Appendix B. Participation (N) in non-sex specific and sex specific areas. Percent of total female and male participants per non-sex specific and sex specific trial type list (Row %). Percent participation of all total trials, non-sex specific and sex specific, listed

	Sex					
	Female		Male		Unknown	
	N (Row %)	% of Total	N (Row %)	% of Total	N (Row %)	% of Total
Non-Sex Specific	52,082 (40.86%)	39.53%	75,376 (59.14%)	57.21%	2 (0.00%)	0.00%
Sex Specific	4190 (97.69%)	3.18%	99 (2.31%)	0.08%	0 (0.00%)	0.00%

Appendix C. Number of participants at US and non-US clinical trial sites, shown by sex at non-sex specific clinical trial sites (n = number of participants)

Sex	Non-Sex Specific, Non-US	Non-Sex Specific, US	Non-Sex Specific, Total
Female	35,367	16,715	52,082
Male	54,695	20,681	75,376
Total	90,062	37,396	127,458

Appendix D. Number of participants at US and non-US clinical trial sites, shown by sex at sex specific clinical trial sites (n = number of participants)

Sex	Sex Specific, Non-US	Sex Specific, US	Sex Specific, Total
Female	852	3338	4190
Male	0	99	99
Total	852	3437	4289

References

[1] U.S. Department of Health and Human Services, F.a.D.A., General Considerations for the Clinical Evaluation of Drugs, (1977).

[2] N. Eshera, G. Soon, E.O. Fadiran, Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA From 2010 to 2012, Am. J. Ther. 22 (6) (2015) 435–455.

[3] R. Poon, S. Umarjee, Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007–2009, J. Women's Health 22 (7) (2013) 604–616.

[4] U.S.G.A. Office, Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement, (2001).

[5] Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products, F.a.D.A. U.S. Department of health and human services, 2013.

[6] A. Chen, H. Itana, et al., Representation of women and minorities in clinical trials for new molecular entities and original therapeutic biologics approved by FDA CDER from 2013 to 2015, J. Womens Health 27 (4) (2017).

[7] S.W. Glickman, E.D. Peterson, et al., Ethical and scientific implications of the globalization of clinical research, N. Engl. J. Med. 360 (8) (2007) 816–823.

[8] A. Gautam, The changing model of big pharma: impact of key trends, 21 Elsevier, 2016, pp. 379–384.

[9] S. Jeong, J. Kim, Current globalization of drug interventional clinical trials: characteristics and associated factors, 2011–2013, Trials 18 (288) (2017).

[10] K. Ayalew, FDA Perspective on International Clinical Trials, (2013).

[11] L.M. Nicholson, J.A. Groner, Recruitment and retention strategies in clinical studies with low-income and minority populations: Progress from 2004-2014, Contemp Clin Trials 45 (2015) 34–40.

[12] Paula M. Frew, Margaret brewinski isaacs, recruitment and retention of pregnant

women into clinical research trials: an overview of challenges, facilitators, and best practices, Clin. Infect. Dis. 59 (Suppl. 7) (2014) S400–S407.
[13] I.o. Medicine, Forum on Drug Discovery, Development, and Translation, (2010) Washington, DC.
[14] Title 21 Vol 5, in Code of Federal Regulations.
[15] L. Nicholson, E.G. Klein, et al., Recruitment and retention strategies in longitudinal clinical studies with low-income populations, Contemp. Clin. Trials 32 (3) (2011) 353–362.
[16] J.A. Clayton, C. Tannenbaum, Reporting sex, gender, or both in clinical research?Reporting sex, gender, or both in clinical ResearchReporting sex, gender, or both in clinical research, JAMA 316 (18) (2016) 1863–1864.